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NEPHROLOGY - ORIGINAL PAPER

Nephrotoxic effects of varenicline as the most effective drug used for smoking cessation: a preliminary experimental study

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Abstract
Purpose Varenicline is a new most effective drug for smoking cessation. Its effect on kidney functions remains unclear. This study purposed to investigate whether varenicline causes nephrotoxicity in rats.
Methods Fifteen rats were randomly assigned to three groups: control, 0.0125 mg kg^{-1} varenicline and 0.025 mg kg^{-1} varenicline (single dose for 3 days, i.p.). Before and after experimental period, serum neutrophil gelatinase-associated lipocalin, creatinine and urea levels were measured. Total oxidant and antioxidant status were measured in kidney homogenates. Histological examination was performed in kidney.
Results The nephrotoxic effects of varenicline were detected by histopathological and biochemical examinations in the varenicline treatment groups. No change was observed in the control group.
Conclusions These findings firstly indicate that a 3-day varenicline treatment causes nephrotoxic effects in rats.

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Introduction

Acute kidney injury (AKI) is defined as a clinical syndrome characterised by a rapid decrease in renal function together with an accumulation of waste products such as urea. The kidneys are the major targets of the toxic effects of various chemical agents, and thus, drug-induced AKI is frequently observed in clinical medicine [1, 2].

Varenicline (Champix© in the UK and Canada; Chantix© in the USA), which is approved in over 80 countries worldwide to date as an aid to smoking cessation in adults, is a highly selective partial agonist of the α4β2 nicotinic acetylcholine receptor (nAChR) and a full agonist at α7 [3, 4]. Varenicline has been associated with neuropsychiatric adverse events (e.g. headache, seizure, fatigue, sleep disorder), gastrointestinal symptoms (e.g. nausea and constipation) and cardiovascular side effects [5–10]. Although a few cases showed the nephrotoxic effects of varenicline, no clinical or experimental study has been conducted on the relationship between varenicline and nephrotoxicity [11–13].

The present study was conducted to determine whether varenicline causes nephrotoxicity in rats.

Materials and methods

Animals and study design

All experimental protocols conducted on the animals were consistent with the National Institutes of Health Guidelines

for the Care and Use of Laboratory Animals (NIH Publication No. 85–23) and approved by the Dumlupınar University Local Ethical Committee (approval number: 2013.08.02; approval date: December 11, 2013). Fifteen male Wistar albino adult (8 months) rats weighing 395 ± 59 g (mean ± SD) were maintained under conditions with temperature of 23 ± 1 °C and relative humidity of 50 % on a 12-h light–dark cycle environment (lights on 7:00–19:00 h) and fed ad libitum with commercially available rat chow and water. The animals were housed per cage (50 cm × 35 cm × 20 cm) and had free access to water and diet. The rats were randomly assigned to the following three groups ($n = 5$ for each group): control (C), 0.0125 mg/kg varenicline-treated group (V1) and 0.025 mg/kg varenicline-treated group (V2). These doses correspond to the daily maximum single dose used for humans, i.e. 1 and 2 mg/80 kg body weight, respectively.

Drugs and chemicals

Varenicline tartrate was purchased from Sigma-Aldrich (Taufkirchen, Germany). Aliquot doses of varenicline were measured for each experiment and dissolved in saline immediately before use. Povidone–iodine was purchased from Adeka (Samsun, Turkey), ketamine was purchased from Ege Vet (İzmir, Turkey) and xylazine was purchased from aniMedica (Senden-Boesensell, Germany).

Anaesthesia and surgical procedure

Before the experimental protocol rats were anaesthetised with a cocktail of ketamine (90 mg/kg) and xylazine (10 mg/kg), 1 mL blood samples were taken from all rats for biochemical assay. The same volume of sterile saline was then injected (i.p.) into the rats for volume replacement treatment. Varenicline was administered to the rats in the V1 and V2 groups (i.p., once a day for 3 days in 0.3 mL sterile saline). The same volume of saline was injected into the rats in the C group during the same time. The rats were anaesthetised again with the same doses of anaesthetic drugs 24 h after the last varenicline or saline injection. The blood samples were taken for biochemical assay. Then, the kidneys were removed. One of the kidneys of each rat was placed in 10 % formaldehyde solution for histopathological assay, and the other was frozen and kept in −80 °C deep freeze until biochemical assay.

Histopathological evaluation

For routine histology, dissected kidneys were fixed in 10 % formalin and embedded in paraffin for serial sectioning through routine tissue examination stages. Then, 5-μm-thick sections were taken and enclosed in paraffin. Sections were stained with periodic acid–Schiff (PAS) to provide the general architecture of the kidneys and to show the loss of brush border in the epithelial cells of the proximal tubule and the thickness of the basal lamina. Tissues were examined, and images were captured using an Olympus BX51 microscope (Olympus BX-51, Tokyo, Japan).

Biochemical assay

Sample collection and preparation

Blood samples were collected into serum separator clot activator tubes (Vacuette®, Greiner Bio-One, Kremsmunster, Austria). All blood samples were allowed to clot for 1 h at room temperature and centrifuged for 20 min at $1000 \times g$. Serum portions were stored at −80 °C until biochemical analysis.

Measurement of biochemical parameters

Serum neutrophil gelatinase-associated lipocalin (NGAL) concentrations were measured with enzyme-linked immunosorbent assay (ELISA) reagent (Cloud-Clone Corp., SEB388Ra, Uscn Life Science Inc., Houston, TX, USA) on a microplate reader (ELX808 Bio-Tek Instruments, Inc., Winooski, VT, USA). The test principle was a sandwich enzyme immunoassay. The microtiter plate provided in this kit was pre-coated with an antibody specific to NGAL. Samples were added to the appropriate microtiter plate wells with a biotin-conjugated antibody specific to NGAL. Avidin conjugated to horseradish peroxidase was added to each microplate and incubated. Afterwards, tetramethyl benzidine solution was added only to wells that contain NGAL. Biotin-conjugated antibody and enzyme-conjugated avidin exhibited a change in colour. The enzyme-substrate reaction was terminated by the addition of sulphuric acid solution. Colour change was measured spectrophotometrically at a wavelength of 450 nm.

Serum creatinine and urea levels were measured by a Roche Cobas c501 analyser (Roche Diagnostics GmbH, Mannheim, Germany) with original reagents. Serum creatinine measurements were taken by kinetic colourimetric Jaffé method. Urea measurements were taken by urease and glutamate dehydrogenase kinetic method. Uric acid measurements were taken by enzymatic uricase colourimetric method.

Renal tissue homogenisates were prepared for total oxidant status (TOS) and total antioxidant status (TAS) measurements. Approximately 1 g renal tissue sample was mixed with 9 mL working solution (50 mmol phosphate buffer, pH 7.40) and homogenised with a mechanic homogeniser. The mixture was centrifuged for 3000 rpm at 5 min. The supernatant was used to obtain TAS and TOS measurements.

TAS measurement was taken by a Roche Cobas c501 analyser (Roche Diagnostics GmbH, Mannheim, Germany) with a TAS kit (Rel Assay Diagnostic, Turkey). With this kit, the reduced ABTS (2,2′-azinobis(3-ethylbenzo-thiazoline-6-sulfonate) molecule is oxidised to $ABTS^{*+}$ using hydrogen peroxide alone in an acidic medium (acetate buffer 30 mmol/L; pH 3.6). In the acetate buffer solution, the concentrated (deep green) $ABTS^{*+}$ molecules remain stable for a long time. While the samples are diluted with a more concentrated acetate buffer solution at high pH (acetate buffer 0.4 mmol/L; pH 5.8), their colour is spontaneously and slowly bleached. Antioxidants present in the sample accelerate the bleaching rate to a degree proportional to their concentrations.

TOS measurement was taken by a Roche Cobas c501 analyser (Roche Diagnostics GmbH, Mannheim, Germany) with a TAS kit (Rel Assay Diagnostic, Turkey). With this kit, oxidants present in the sample oxidise the ferrous ion–o-dianisidine complex to ferric ions. The oxidation reaction is enhanced by glycerol molecules, which are abundant in the reaction medium. The ferric ions make a coloured complex with xylenol orange in an acidic medium. The colour intensity, which can be measured spectrophotometrically, is related to the total quantity of oxidant molecules in the sample.

Statistical analysis

TAS, TOS and OSI values of the experimental groups were compared using one-way ANOVA and post hoc Tukey tests (SPSS 16.0). Paired *t* test was used to compare NGAL, urea and creatinine levels before and after the experimental protocol of each group.

Results

Histological findings

Examples of the kidney histopathology are shown in Fig. 1. The histological examination of the kidneys of the untreated control rats showed normal kidney morphology. Glomerular structures in the cortex were regular, and Bowman's cavity was normal. PAS staining indicated a remarkable obliterated Bowman's space. Mononuclear infiltrating cells were observed in some fields in the V1 group. Moreover, tubular damage was observed in the cells lining a few cortical tubules. Brush border edges of the proximal curved tubule were damaged in the V2 group. Leucocyte infiltration and tubular dilatation were observed, and the parietal layer of the Bowman's capsule was thickened compared with that of the control group (data not shown). Furthermore, corpuscles with completely and partially obliterated Bowman's space were found in both varenicline-treated groups.

Biochemical findings

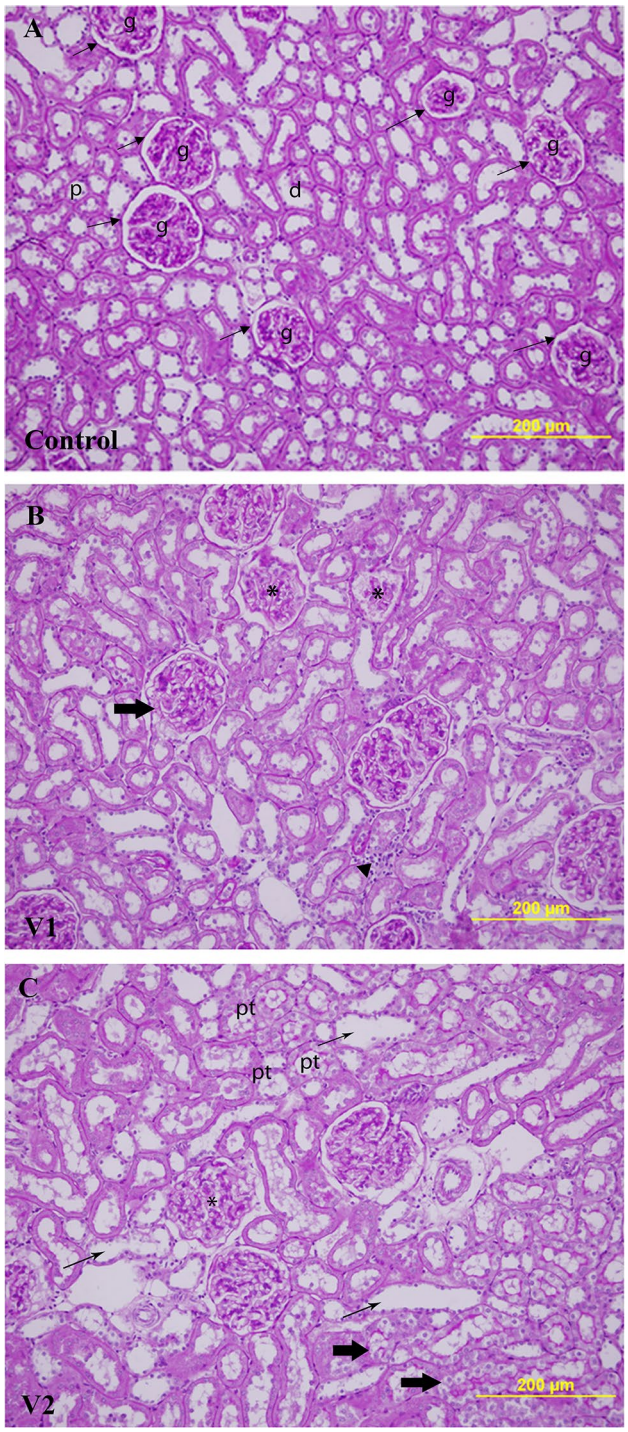
NGAL, urea and creatinine levels after varenicline treatment significantly increased unlike those before varenicline treatment in the V1 and V2 groups. No significant differences were found between before and after values of NGAL, urea and creatinine in the C group (Table 1).

TAS level of the V1 group was significantly higher than that of the V2 group. TOS level of the V1 group was significantly higher than that of the C group. OSI level of the V2 group was significantly higher than that of the C group (Table 2).

Discussion

The current study indicated that a 3-day varenicline treatment caused nephrotoxicity in rats. The nephrotoxic effects of varenicline were detected by histopathologic and biochemical examinations in the varenicline treatment groups; no change was observed in the control group. To our knowledge, this is the first study demonstrating that varenicline treatment causes nephrotoxic effects.

Three cases of the nephrotoxic effect of varenicline were reported. In the first report, a 53-year-old white male with pre-existing moderate renal insufficiency was admitted to the hospital for acute renal failure following an increase in serum creatinine (10.6 mg/dL). One week prior to admission, aside from all other medications, the patient started taking varenicline (dose not mentioned) for smoking cessation. However, 2 weeks after varenicline was discontinued with no other changes in therapy, the serum creatinine level of the patient decreased to 6.4 mg/dL [11]. The other case of a 64-year-old man with a history of chronic renal insufficiency secondary to hypertension and remote post-operative kidney injury was referred to an outpatient nephrology clinic after developing acute on chronic renal insufficiency. In this case, renal functions worsened during the varenicline therapy (serum creatinine level increased from 1.4 mg/dL at baseline to 2.6 mg/dL). The use of varenicline was discontinued, and oral prednisone therapy was administered. Three weeks later, the serum creatinine level of the patient decreased to 1.8 mg/dL [12]. In the last case, a 56-year-old female with nephrotic syndrome took varenicline for 3 months during the time when her kidney function deteriorated. When she stopped the varenicline, her creatinine level dropped to 200–250 μmol/L from 319 umol/L [13]. Although the findings of these cases are consistent with our results, these patients had a few confounding factors, such as the use of multiple medications and



◀ **Fig. 1** PAS staining of all groups. **a** Normal histological structure was seen in the renal cortex in the control group. Malpighian renal corpuscle containing a glomerulus (*g*), parietal layer of Bowman's capsule (*arrow*), proximal convoluted tubules (*p*) and distal convoluted tubules (*d*) in the control group. Histological abnormalities were seen in other groups. **b** Seven corpuscles with patent Bowman's space and several tubules with vacuolated cytoplasm of the lining cells in the 0.0125 mg varenicline-treated group (V1). Interstitial inflammation (*arrowhead*), corpuscles with completely obliterated Bowman's space (*stars*), a corpuscle with partially obliterated space (*thick arrow*). **c** Proximal tubule with destroyed brush border (*pt*). *Stars* in (**c**) indicate focally destroyed epithelial cells with empty cytoplasm, dilatation of distal tubule (*thick arrow*) and corpuscles with completely obliterated Bowman's space (*star*) in the 0.025-mg varenicline-treated group (V2) (renal cortex; PAS, ×200)

already existing diseases (membranous glomerulonephritis, chronic renal insufficiency, moderate kidney dysfunction, diabetes mellitus and hypertension). However, no clinical or experimental studies on the relationship between varenicline and nephrotoxicity have been conducted yet.

Although several mechanisms have been suggested, the underlying cause of drug-induced nephrotoxicity still remains unclear. Several major mechanisms, such as tubular cell toxicity, oxidative stress, inflammation, changes in glomerular hemodynamics, crystal nephropathy, rhabdomyolysis and thrombotic microangiopathy in the kidney, have been suggested for drug-induced AKI [14, 15].

NGAL, also known as lipocalin 2 or *lcn2*, is indisputably the most promising novel AKI biomarker. It is expressed in several human tissues at very low levels and markedly induced in damaged epithelial cells (including the kidney, colon, liver and lung). Preclinical studies revealed NGAL to be one of the most upregulated genes immediately after AKI and highly induced proteins after ischaemic or nephrotoxic AKI in animal models [16, 17]. NGAL, as a non-invasive biomarker in human AKI protein, is easily detected in the urine immediately after AKI. A marked increase in urine and serum NGAL was documented compared with normal controls in a cross-sectional study [17]. Both urine and plasma NGAL were excellent independent predictors of AKI, and NGAL expression increased in the proximal tubule cells by drug-induced nephrotoxicity [14, 17]. In this study, after varenicline treatment and consistent with the increase in NGAL level, an increase was also observed in urea and creatinine levels as indicators of renal function. Aside from the biochemical findings, our histopathological results revealed that varenicline caused tubular damage. Consistent with our histopathological findings, varenicline-induced tubular damage was observed histopathologically in a previous case report [12].

Varenicline is a non-nicotine agent. It is a partial agonist highly selective for nAChRs [18]. Several nAChR subunits are expressed in normal kidneys. Nicotine increases the severity of renal injury in animal models, such as AKI, diabetes, acute nephritis and subtotal nephrectomy [19]. NAChRs are known to play a role in inflammation [20]. In this study, the inflammatory signs were observed in a histological evaluation in the varenicline-treated groups. Another mechanism of varenicline-induced nephrotoxicity may be formed by nAChR-mediated inflammation.

Renal tubules, especially proximal tubule cells, are exposed to drugs in the process of concentration and

Table 1 Effect of varenicline treatment on parameters of renal function

	C		V1		V2		*P**
	Before saline	After saline	Before varenicline	After varenicline	Before varenicline	After varenicline	
NGAL	12.06 ± 1.47 (10.48–13.88)	13.87 ± 2.47 (10.98–16,67)	13.14 ± 2.47^{A} (10.13–16.83)	25.56 ± 4.05^{A} (20.07–30.22)	41.03 ± 13.57^{B} (23.76–55.99)	156.03 ± 46.79^{B} (96.58–220.04)	A: 0.002 B: 0.004
Urea	47.2 ± 8.90 (63–58)	46.4 ± 8.96 (38–58)	41.6 ± 3.36^{C} (38–47)	50.8 ± 2.78^{C} (47–54)	45.80 ± 3.35^{D} (42–50)	53.60 ± 4.10^{D} (50–58)	C: 0.000 D: 0.009
Creatinine	0.44 ± 0.09 (0.31–0.54)	0.48 ± 0.1 (0.36–0.62)	0.43 ± 0,07^{E} (0.34–0.50)	0.50 ± 0.07^{E} (0.42–0.58)	0.48 ± 0.07^{F} (0.39–0.59)	0.53 ± 0.05^{F} (0.49–0.61)	E: 0.000 F: 0.033

Values are expressed as mean ± SD (min–max); $N = 5$

C Control group, V1: 0.0125 mg/kg varenicline treatment group, V2: 0.025 mg/kg varenicline treatment group

* According to the Student's *t* test. $P \geq 0.05$ for *P* values are not given

Table 2 Effect of varenicline treatment on renal tissue oxidant/antioxidant parameters of rats

	C	V1	V2	*p**
TOS (μmol H_2O_2 Eq/L)	16.49 ± 0.83^{A} (15.31–17.48)	21.22 ± 4.39^{A} (16.72–27.72)	19.68 ± 0.78 (18.56–20.63)	A: 0.036
TAS (mmol Trolox Eq/L)	1.99 ± 0.12 (1.87–2.18)	2.19 ± 0.29^{B} (1.73–2.55)	0.71 ± 0.15^{B} (1.50–1.86)	B: 0.008
OSI (arbitrary unit)	8.34 ± 0.80^{C} (7.02–9.14)	9.76 ± 1.72 (7.47–11.44)	11.56 ± 1.20^{C} (10.5–13.44)	C: 0.005

Values are expressed as mean ± SD (min–max); $N = 5$

* According to the one-way ANOVA test. $P \geq 0.05$ for all comparisons for which *P* values are not given

reabsorption through the glomerulus. They are greatly influenced by drug toxicity. Cytotoxicity occurs because of damaged mitochondria in the tubules, disturbed tubular transport system and increase in oxidative stress by free radical generation [14]. High production of reactive oxygen species and resulting oxidative stress can contribute to the mechanisms of AKI development [21]. Consistent with previous reports, oxidative mechanisms could have mediated the nephrotoxic effect of varenicline because the oxidative stress level increased in the varenicline-treated rats in the current study.

Varenicline, which exists as a cation at physiological pH, is mainly excreted in urine as an unchanged form in humans and animals. The principal secretion of cationic drugs in the renal brush border membrane is mediated by the MATE transporter [22]. Renal brush border damage was found in our histolopathologic examination. Damage to varenicline-excreting localisation implies that the damage may be caused by this drug.

In smoking cessation therapy, dosing of varenicline starts at 0.5 mg once daily for the first 3 days and then increases to 0.5 mg twice daily for the following 4 days and 1 mg twice daily thereafter, for a total of 12 weeks [23]. Every day of the life of a rat has been suggested to be equivalent to 30 days of human life [24]. Therefore, a 3-day (equivalent to 12 weeks) treatment protocol was applied in this study. The reason for choosing 0.0125 and 0.025 mg/kg doses in this study design is that the doses are equivalent to the daily maximum single dose used for humans, i.e. 1 mg/80 kg and 2 mg/80 kg body weight, respectively. In healthy adults, the maximum plasma concentration of varenicline occurs within 3 to 4 h of a single dose of oral administration, and steady-state concentration is typically reached within 4 days following regular doses. The elimination of varenicline is mainly through the kidneys. The elimination half-life is approximately 24 h, and this elimination rate can contribute to an increase in plasma levels of varenicline [25–27]. As plasma concentration is higher in regular doses of varenicline than in a single-dose treatment, the possible adverse effects of varenicline may increase in regular doses [25, 27]. Although the pharmacokinetic properties of varenicline in rats and humans are similar, some differences may be present between the two, such as the pharmacodynamic properties of varenicline [26].

There are some limitations of this study. First, although nephrotoxic effect of varenicline as a nicotinic receptor agonist has shown in this study, the nephrotoxic effect of nicotine with application of varenicline was not investigated. Since varenicline is a pharmacological agent used in the treatment of nicotine dependence, the nephrotoxic effect of

varenicline in an experimental nicotine dependence model may be a valuable research subject for a new study. Second, the drug dose–response curve was not obtained. Because, the effects of only two doses of varenicline were measured in a single time. In new studies, it may be possible to investigate the effectiveness of different doses of varenicline and nicotine in different time points. Another limitation, not only NGAL, but also cysteine proteinase inhibitors C (Cys-C), kidney injury molecule-1(KIM-1) and urinary interleukin 18 (uIL-18) could be measured for early diagnosis of AKI in this study. NGAL is an early increased biomarker rather than the others (Cys-C, KIM-1, uIL-18) in various clinical situations [28]. It appears to be the most promising of all biomarkers. Performance of NGAL has been comparable or better than other biomarkers [29]. For these reasons, we preferred only NGAL in our study.

Conclusions

In conclusion, the findings of this study firstly show that a 3-day varenicline treatment causes nephrotoxic effects in rats. Although our findings imply that the nephrotoxic effects of varenicline are mediated by oxidative stress and/or inflammatory processes, the mechanisms allotted to the nephrotoxic effects of varenicline are not fully elucidated at this stage. However, nephrotoxicity may be added to the potential side effects of varenicline according to our findings. When doctors prescribe varenicline, patients should be assessed in detail in terms of impaired renal function risk factors, and patients with high-risk factors should be closely followed up.

Conflict of interest The authors declare that they have no conflict of interest.

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